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The clinical significance of gastric acidity

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THE CLINICAL SIGNIFICANCE OF
GASTRIC ACIDITY

Senior Thesis

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THE CLINICAL SIGNIFICANCE OF GASTRIC ACIDITY

Historical

Our present knowledge of the acidity of the gastric secretion and its significance is based upon the contributions of many careful workers of the last three hundred years. *omit.*

The earliest evidence we have of the knowledge of acid in the stomach is the work of Van Helmont (1577-1644). He made an analysis of the process of fermentation and, applying this principle to human physiology, believed that food and drink in the stomach were changed to chyle through a process of fermentation, similar to the evolution of gas from the juice of grapes (cited in 41). He recognized the contents of the stomach to be acid and attributed this reaction to his ferment. Franciscus Sylvius (1614-1672), a student of Van Helmont, carried on this work and supposed that digestion was a chemical fermentation involving the union of acid and alkaline qualities (cited in 41).

The first scientific observations on the gastric juice were made by Rene de Reaumur (1683-1757). This work was carried out on a pet buzzard, which was made to swallow cylinders containing food. These cylinders were brought up again by means of an attached string and showed the solvent action of the gastric juice. By means of a sponge he removed gastric juice from the stomach which he described as an opaque cloudy fluid, yellowish white in color, with a salty acid taste (cited in 41 and 90).

Abate Spallanzani (1729-1799) repeated Reaumur's experiments and collected large amounts of juice by this method. He studied

his own vomitus but was not able to obtain pure gastric juice because he could not force himself to vomit on an empty stomach. Spallanzani failed to recognize the significance of the acid reaction of the gastric contents and looked upon this as an abnormality (cited in 41).

A little later, John Hunter (1728-1793) observed the partial digestion of the lining of the stomach at autopsies (52). In his writings he attached importance to the acidity of the juice but supposed that the acid appeared only after death.

The first man to recognize the true physiological significance of the acid in the stomach was John Richardson Young (1782-1804). He emphasized the acid character of the gastric juice in dogs and expressed the belief that digestion could not occur in the absence of acid (cited in 41). Chemical tests led him to believe that this was phosphoric acid.

William Prout (cited in 41) was the first to demonstrate the nature of the acid found in the stomach. He proved that hydrochloric acid existed in the gastric juice of many animals. In examining the vomitus of a dyspeptic woman, he obtained similar results.

Immediately after Prout, Graves in Ireland found lactic acid in the emesis of patients complaining of dyspeptic symptoms, concluding that lactic acid was found in all body fluids and that its secretion was greatly increased in disease conditions (cited in 90).

Following this there was a long controversy among investigators regarding the exact nature of the acid in the stomach. The problem was finally settled in 1852 by Biddler and Schmidt (cited in 90) who demonstrated that the excess of chlorides over the estimated bases was

sufficient to account for the acidity of the juice.

Probably the most important of the earlier contributions on the physiology of the stomach is the classical work of William Beaumont (3 and 4). In 1822 at Michillimacinac, Michigan Territory, Alexis St. Martin was accidentally wounded by the discharge of a blunderbuss two feet from his body. The charge entered his left side, penetrating the thorax and abdomen. Beaumont, who was stationed at the post, took care of the wound. Fortunately, St. Martin recovered but he developed a permanent external gastric fistula. Beaumont seized upon this unusual opportunity and for the next three years made observations concerning the chemical and digestive properties of gastric juice.

It might be well to quote some of his observations to show the accuracy and thoroughness of his work. "The quantity of aliment is probably of more importance than the quality to insure health. The system requires much less than is generally supplied to it. The stomach disposes of a definite quantity. If more be taken than the actual wants of economy require, the residue remains in the stomach and becomes a source of irritation and produces a consequent aberration of function, or passes into the lower bowels in an undigested state and extends to them its deleterious influence. Dyspepsia is oftener the effect of over-eating and over-drinking than any other cause." "Derangement of the digestive organs, slight febrile excitement, fright, or any sudden affection of passions, causes material alterations in its (gastric juice) appearance."

With one or two exceptions his deductions are accepted even today. Some of his conclusions are:

1. The agent of chymification is gastric juice.
2. It acts as a solvent of food and alters its properties.
3. It contains free muriatic acid and other active chemical principles.
4. The gastric juice is never found free in the gastric cavity but always is excited to discharge itself by the introduction of food or other irritants.
5. It is capable of combining with a certain fixed quantity of food; when more aliment is presented for its action than it will dissolve, disturbances of the stomach or indigestion will ensue.

After Beaumont the next great name in the development of our knowledge of gastric secretion and gastric acidity was that of Pavlov. Following up Beaumont's methods of study, Pavlov in 1889 produced artificial gastric fistulae in dogs (84). He further extended this work by dividing the esophagus, making a complete anatomical separation between the cavities of the mouth and the stomach. Then upon feeding the dogs, the food dropped out the proximal portion of the esophagus and pure gastric juice, which was secreted in the stomach, was then studied through an artificial fistula.

To study the secretion during digestion was another problem. With this idea in mind, Heidenhain produced a pouch at the pyloric end of the stomach communicating with the surface of the abdomen.

Pavlov (84) modified this procedure so as to preserve the nerve supply to the isolated portion. In this manner pure gastric juice could be obtained and studied during the process of digestion within the stomach itself.

The development of our modern clinical methods of studying the gastric juice followed the use of the stomach tube. Physick in 1812 was the first to use a tube on human beings to remove the contents of the stomach. Although he is credited with the invention of the stomach tube, it had been used for years to pass medication into the stomach (cited in 90).

Von Leube (cited in 74 and 90) in 1871 introduced the use of the stomach tube for analytical or diagnostic purposes. Ewald and Boas extended this work. Using von Leube's technique, Ewald and Boas in 1885 developed the idea of a constant stimulus and devised a standard test meal, thus enhancing the use of the stomach tube (33). The standard test breakfast still used today consists of a roll or piece of bread or toast (35 grams) and two cups of water or tea (10 ounces).

Rehfuss (87) developed the soft rubber catheter tube by modifying the Einhorn duodenal tube. He also developed the fractional analytical test, showing a curve of the gastric secretion during the entire digestive cycle rather than the activity at only one level (88).

In the last thirty years much work has been done regarding the stimulation of gastric secretion by specific hormones. This has

developed clinically into the use of histamine in gastric analysis.

Edkins (29) in 1906 was the first to demonstrate a hormone in the stomach which he called gastrin. He found that extracts made from the pyloric mucous membrane in boiling water or hydrochloric acid contained an active substance which on injection into the blood vessels of an animal led to the secretion of gastric juice. He found also that extracts made from the mucous membrane of the fundus did not contain this substance. Furthermore, he believed that this substance was not a ferment or an enzyme, as boiling the extract led to an increase rather than a diminution of its properties.

In 1920, Koch, Luckhart and Keeton (29) noted a striking similarity between histamine and gastrin in their action on gastric secretion in the dog. In the human, the effect of histamine on the stomach was first observed by Carnot, Koskowski and Lubert in 1922 (11). They found that the injection of small amounts of the drug subcutaneously was followed by an increase in the flow of gastric juice with an absolute increase in free acidity and in total acidity.

Following these observations, histamine was used clinically in gastric studies. Matheson and Ammon (75) observed its effects upon twelve consecutive patients. They found an increase in acid concentration starting in fifteen minutes after its injection, reaching a maximum in one-half to one hour. Gumpertz and

Voorhaus (43) called attention to the value of histamine as an agent of differentiating between true and pseudo-achylia.

Ivy and his associates seem to have definitely established a relationship between gastrin, as found in the pyloric mucosa, and histamine. In 1931, Sacks, Ivy, Burgess and Vandolgh_a (92) reported the isolation of histamine from the pyloric mucosa of the hog. This was obtained in crystalline form as a sulphate. Later evidence by the same authors (93) shows that histamine is the only gastric secretory excitant present in extracts of the pyloric mucosa which is active subcutaneously. Their conclusion is that the evidence indicates either that histamine is the gastric hormone, or if not, there is no gastric hormone, or the gastric hormone has never been extracted from the pyloric mucosa.

THE COMPONENTS OF GASTRIC ACIDITY

The acid properties of the gastric juice are due to the presence of hydrochloric acid which may be found both in its free state or in combination with protein substances, as protein salts. Lactic acid, fatty acids and even carbon dioxide will give acid reactions which affect the total acidity, but they are physiologically of minor importance (6).

Hydrochloric acid is secreted into the stomach along with pepsin by the glands of the mucosa. The glands of the stomach are of three types: the cardiac, the fundic and the pyloric glands. The fundic glands, however, are found not only in the fundus but occupy

the greater part of the body of the stomach as well (77). It has been definitely established that the hydrochloric acid of the stomach is secreted by the fundic glands. They are arranged perpendicularly to the surface of the mucosa, penetrating its entire thickness to a depth varying from 0.5 m.m. to 1/5 m.m. The upper part of this space is occupied by the foveolae or gastric pits, into the bottom of which the glands open in small groups. The total number of these glands is estimated at 35,000,000.

In the fundic glands there are four types of cells: (a) The chief cells, forming a simple layer on the inner surface of the basement membrane and lining the lower half of the glandular tubule; (b) The parietal cells, scattered singly between the chief cells throughout the whole length of the gland, occupying a position more peripheral between the chief cells and the basement membrane; (c) The mucous neck cells; and (d) The argentaffine cells (77).

It has been shown that the hydrochloric acid of the gastric juice or at least its precursor is formed within the parietal cells of these glands. Fitzgerald (39) investigating this question, injected into rabbits a solution containing equal parts of ammonium ferric citrate and potassium ferrocyanide and then made microscopic studies to determine the presence of Prussian blue in the glands of the gastric mucosa. His conclusions based on these studies were that the cytoplasm of the parietal cells formed the free acid within the cell itself. "It may be said in

conclusion, that the occurrence of Prussian blue, not only in the lumen of the gland tubules, but also in the canaliculi of the parietal cells, makes it certain that the hydrochloric acid is at least already formed and free in the secretion as it appears in the canaliculi. Whether the acid occurs in the cytoplasm of the cell still remains an open question although the very faint blue occasionally observed in a parietal cell seems to postulate an affirmative.....The occurrence of free acid in the canaliculi and also in certain cases in the lymphatic vessels between the gastric tubules, is therefore best explained by supposing that the cytoplasm of the parietal cells forms in itself the free acid and under ordinary conditions that the free acid so formed diffuses into the canaliculi."

Bensley and Harvey (25), however, showed that the secretion within the parietal cells is slightly alkaline, whereas that in the lumen of the gland proper is very nearly neutral. Therefore, they say that the acid is formed entirely above the level of the gland proper in the faveolae and on the surface. They have advanced the theory that the parietal cells secrete a chloride of an organic base, this compound yielding free hydrochloric acid as it reaches the gastric faveolae.

Dawson and Ivy (25), working on this problem, confirmed the observations of Bensley and Harvey. These authors maintained physiological relationships by performing their investigations on Pavlov Pouch-dogs and demonstrated that the canaliculi and

cytoplasm of the active parietal cells were alkaline to cyanamin and acid to neutral red (p H 3.0 to 6.8).

The chemical reaction involved in the formation of acid by the gastric cells is unknown. The sodium chloride of the blood is undoubtedly involved. Maly suggested that this might react with monosodium acid phosphate in the cells to form H Cl and di-sodium acid phosphate. The latter might be converted back to acid by carbon dioxide (47). Mathews supposes that hydrochloric acid might be set free by hydrolysis from combination with some weak base such as ammonia (76). Another explanation is that free phosphoric acid valences may be set free by the enzymic hydrolysis of organic phosphoric acid esters (47). Hanke advances the theory that organic chlorides are split by a special enzyme in the gastric mucosa (44).

The chief role of hydrochloric acid in the stomach is to activate protein digestion. Pepsin is formed as a pro-enzyme or pepsinogen. This is immediately converted into pepsin by contact with hydrochloric acid. Pepsin is not active in neutral or alkaline solutions but requires a certain degree of acidity before performing its proper function. The percentage of acidity which is most effective for the action of pepsin varies with the protein to be acted upon, 0.08 to 0.1 per cent. for fibrin and 0.25 per cent for egg white (89).

Besides forming an optimum medium for the action of pepsin, hydrochloric acid acts as an antiseptic or germicide which prevents putrefactive processes in the stomach (47). When the hydrochloric

acid in the gastric juice is diminished or absent, there is no check to the growth of micro-organisms in the stomach. A condition of hypo-acidity may also give rise to fermentation in the stomach with the formation of comparatively large amounts of lactic acid.

The acidity of the gastric juice as it is secreted by the glands during digestion is 0.4 to 0.5 per cent. hydrochloric acid. The acidity of the juice as secreted is constant and independent of the rate of secretion (49) (12) (84). Hollander and Cowgill found the maximum p H of the gastric secretion to be about 0.9 (49). Menten (78) reports the normal juice as secreted to have a p.H 1.3 (50). When the contents of the stomach are examined during digestion, however, the concentration of the hydrochloric acid is much lower, varying around 0.2 per cent., this being the optimum for pepsin activity. This decrease is due to various factors, such as regurgitation of alkaline fluid from the intestines, by ingested food, and by alkaline secretions from the pyloric end of the stomach and mucous glands, which will be discussed in detail later.

Rehfuss, Bergheim and Hawk (88) (89) made an exhaustive study to determine a normal acidity curve which could be used as a standard in the recognition of pathological conditions. In their investigations, they made over a thousand complete fractional gastric analyses on medical students who were apparently normal so far as gastro-intestinal ^{SYMPTOMS} showed. These tests were made using a great variety of foods, and the results of fifteen minute samples were

carefully plotted.

They showed that the digestive phase may be divided into three parts:

(a) The first is the period of adjustment or rise. This is the most unstable phase of all and one in which there is a poor admixture of food in the stomach. During this phase all phenomena of the interdigestive period are lost. The secretion increases in velocity and in acidity and there is a period of disequilibrium lasting for about 30-40 minutes. During this period there is an attempt on the part of the stomach to reach equilibrium, both secretory and motor. It is the safe transit through this phase that often constitutes good or bad digestion because this is by far the most unstable period of digestion.

(b) The middle or second phase is the digestive "acme" or full tide of gastric digestion. In this period both the motor and secretory functions of the stomach are at their height and the normal optimum is reached. During this stage we probably have the highest period of dissociated free hydrochloric acid and therefore the most effective in gastric digestion. In disease, this period may be enormously prolonged.

(c) The terminal or third stage is normally one of decline or the stage of readjustment to the approaching interdigestive phase. From the standpoint of pathology this is probably the most important stage in gastric digestion. Here we have a falling off of the secretory velocity and acidity with an increasing

tendency to duodenal regurgitation, gradually resuming the interdigestive phase. Normally, there should be a gradual decline with a gradual reappearance of all the phenomena of the interdigestive phase.

From these observations we find the following points to be of importance in the interpretation of the acidity curve:

1. The period of ascent. This usually occupies the first 30 - 40 minutes and indicates the rapidity and intensity of the response to a known stimulus.

2. The character and height of the "acme", whether it is accelerated or retarded and whether it is abrupt or sustained.

3. The rapidity and regularity of the descent.

In this work Rehfuss and his associates found that there is no specific curve for the normal person which would hold in all cases. Rather they found that normally there were three types of curves, depending upon the rapidity of reaction to a given stimulus, the height of the curve and the descent of the curve:

1. The iso-secretory type shows a steady rise, a high point in total acidity (expressed in terms of tenth normal sodium hydroxide) of 60 usually sustained from one-half to one hour and then a gradual decline to the interdigestive phase in two to two and a half hours. The curve is steady and unbroken, the high point usually rounded and not abrupt and usually found at about one hour.

2. The hypersecretory type shows a rapid response with a rapid increase in acidity, a high point of 70 to 100 or over, either sustained or abrupt and a slow decline, or none at all, in the usual time.

3. The hyposecretory type gave a slower ascent than usual, a slower response to stimuli and a high point from 40 to 50.

A continued secretion was found in many who should be described as normal. Although food left the stomach in two to two and a half hours, there was still an outpouring of pure gastric juice for a half hour, an hour, or even several hours. This occurred in normal symptomless persons.

In Rehfuess' own words, "There is a group, by no means small, in which the secretion is very abundant, the acid figure high and there is often a post-digestive or continued secretion. These people almost always react in this way, while there is a group diametrically opposed, who show a rather tardive response. Both are normal, both without symptoms; both must be considered in the analysis of any pathological case." (88)

Bennett and Ryle (6) attempted to establish a normal curve for a standardized stimulus to be used for clinical diagnosis. Fractional analyses were made in 100 healthy medical students who had been given a standard gruel meal. They, too, found wide variations of normal response to the same meal, with a group giving a "hypersecretory" type of curve and another a "hyposecretory" curve. In this series, they found that in eighty per cent. the free hydrochloric acid fell to practically nil immediately following the meal and subsequently rose to a height below 50 and then fell away again. The result of their investigation is shown in Figure 1,

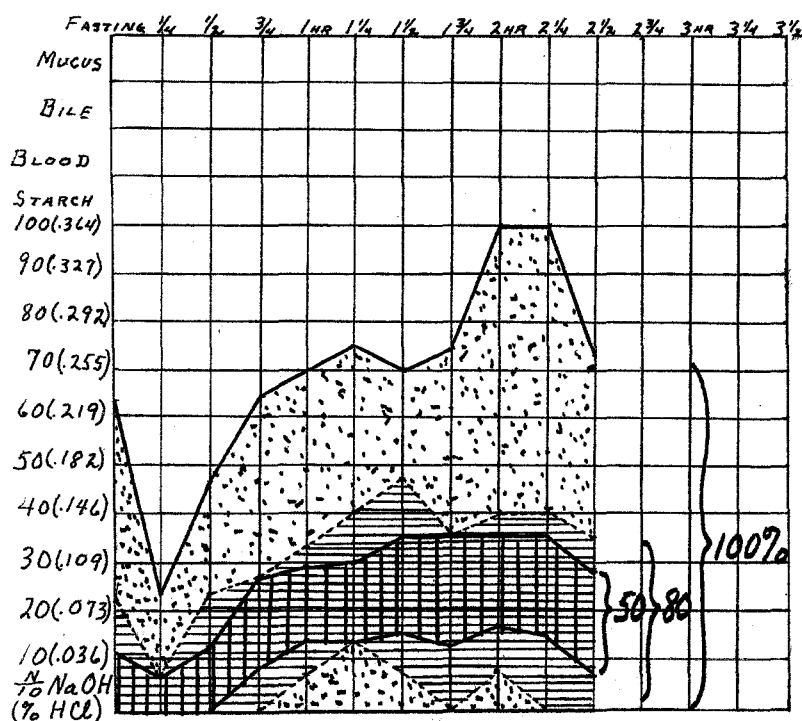


Figure 1.

showing the ranges in which 50 per cent., 80 per cent., and 100 per cent. of their normals fell. Figure 2 is Bennett and Ryle's standard chart which shows the ranges for 80 per cent. of all normal responses to the standard gruel meal.

The work of Bennett and Ryle is of more practical value than that of Rehfuss because they have dealt with variations in acidity using one standardized stimulus, while Rehfuss and associates used all varieties of food. However, if we were to construct charts from Rehfuss' work on the basis of bread and cereals, the findings would be the same. Rehfuss also states that a test meal of tea and toast (Ewald meal) would give similar findings to Bennett and

Ryle's gruel meal and for clinical purposes that is of value (89).

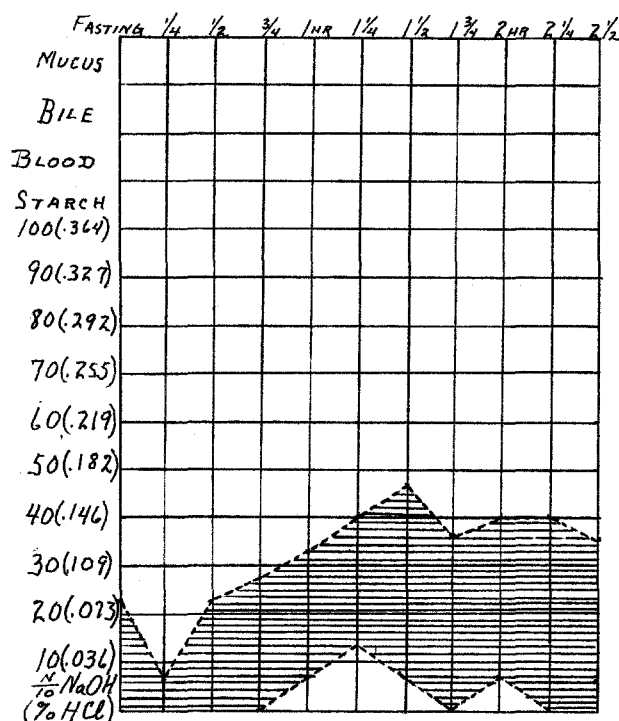


Figure 2.

Campbell, ^F_Baird and Hern (2) in the examination of fifty-seven normal students obtained the same general results as Bennett and Ryle on the range of acidity of the gastric juice after gruel meal. They found outside of this group that hypochlorhydria or achlorhydria is more likely to occur in men leading sedentary lives and is apt to be accompanied by rapid emptying, but hyperchlorhydria is more common in men leading more active lives and associated with delayed emptying.

Beaumont (17) although most of his observations were accurate

and valuable, was responsible for advancing the erroneous view that there is no secretion of gastric juice in the absence of food in the stomach. Since his time it has been generally established that there is a continuous secretion in the stomach whether food is present or not. This continuous secretion is what Carlson terms "hunger" or "fasting" secretion.

According to Carlson (16) the appetite or the digestion juice shows a constant total acidity or nearly 0.5 per cent. when secreted beyond a certain minimum rate. The hunger or fasting juice, however, (as well as appetite juice secreted at a low rate) shows a lower acidity of 0.2 per cent. or less. He states that the greater the secretion rate of the hunger juice, the higher the acidity, until it may equal that of the appetite juice. From these observations, Carlson disagrees with Pavlov and believes the acidity of the gastric juice as secreted depends upon its rate of secretion.

There are many factors influencing the amount and rate of secretion of hydrochloric acid in the stomach. Even before the normal stimulus for secretion comes in contact with the stomach there is what is known as psychic secretion. Bitter and Schmidt (79) first observed that the mere sight of food called forth gastric secretion in the dog. It remained for Pavlov some forty years later to establish more definitely the character of the psychic secretion of gastric juice (84). He pointed out that such a secretion was the normal initiator of gastric digestion in dogs and might be induced by the sight, smell, taste, mastication, or the thought of food

or even through the stimulation of appetite by the presence of solid matter in the stomach.

Carlson, however, pointed out what he believed to be a source of error in earlier investigations (16). He held that no secretion could be produced in the human by the thought of food, that the secretion produced by the smell or sight of food was relatively slight or inconstant and that the significant appetite secretion was produced by the chewing and tasting of good food.

Pavlov believed the psychic secretion to be of great importance in initiating gastric digestion. Carlson, however, discounted this because he found that the continuous secretion in the stomach served a similar purpose and that elimination of the psychic secretion produced no indigestion.

Miller, Bergeim, Rehfuess and Hawk (79) made the following observations from their investigation conducted on normal medical students.

1. Sight of food alone gave rise to a distinct secretion of gastric juice.
2. The sound and thought of frying steak gave rise to gastric secretion.
3. The maximum appetite secretion was produced by a combination of these factors--tasting, chewing, smelling and seeing palatable food.
4. Anxiety and mental strain delayed gastric digestion although the acidity level remained high for a long time. This observation shows that it is not at all surprising that worry aggravates a condition of gastric ulcer.

Sim, Ivy and McCarthy (66) have found that it is possible to stimulate gastric secretion by mechanical distension of the stomach. They showed that liquids and foods in quantities sufficient to induce distension in the stomach produce mechanical secretion. The idea of distension of the stomach producing a stimulation of the mucous membrane can be proved by injection of large amounts of air through a stomach tube, which will usually result in the appearance of an increased amount of secretion.

These authors further showed (67) that the presence of certain food products, such as peptones, amino acids and amines, in the duodenum will also give an increase in gastric secretion. These experiments were performed on dogs with isolated stomach pouches. Garbat, by double gastro-duodenal intubation, has demonstrated the same thing in man and his experiments have been confirmed by Rehfuess (89).

Ivy and his associates divide the secretion of gastric juice during digestion into three phases.

1. The cephalic phase, demonstrated by Pavlov as the psychic secretion, which is excited chiefly by the taste, smell and mastication of palatable food and even by the sight or hypnotic suggestion of food. They reject the term "psychic secretion" because it is not necessarily psychic and has been shown to occur in the absence of a cerebral cortex.
2. The second or gastric phase, according to these authors, is characterized by mechanical and chemical stimuli in the stomach.

3. The third or intestinal phase is that produced by the presence of the stimuli acting in the bowel.

Rehfuss shows the clinical significance of this conception (89):

"It would seem likely that exaggeration of the gastric secretion during the first hour of digestion might be dependent upon an exaggeration of the cephalic phase or a combination of the gastric and cephalic phases.

"Increased secretion might likewise argue for the undue irritability of the gastric nerve mechanism on one hand, or to an excitability of the mucous membrane on the other. The exaggeration of the terminal stage of digestion or the tardive hyperacidity, however, would seem today more intimately linked up with the intestinal phase of digestion, and this is altogether likely if we realize how frequently this latter exaggeration is associated with conditions of the duodenum and other organic disturbances which are outside the stomach. It would, then, seem that true gastric conditions would result in an exaggeration of the middle portion of the digestive phase owing to the undue effect of material in the stomach which ought to stimulate the mucous membrane."

During digestion, the type of food taken is an important factor in the stimulation of hydrochloric acid. Rehfuss and his associates (89) in a series of investigations over a period of almost nine years, have made many interesting observations on the secretory response to various types of foods. They found that foods high in protein show the highest acidity, with carbohydrate foods in general producing low acid secretion.

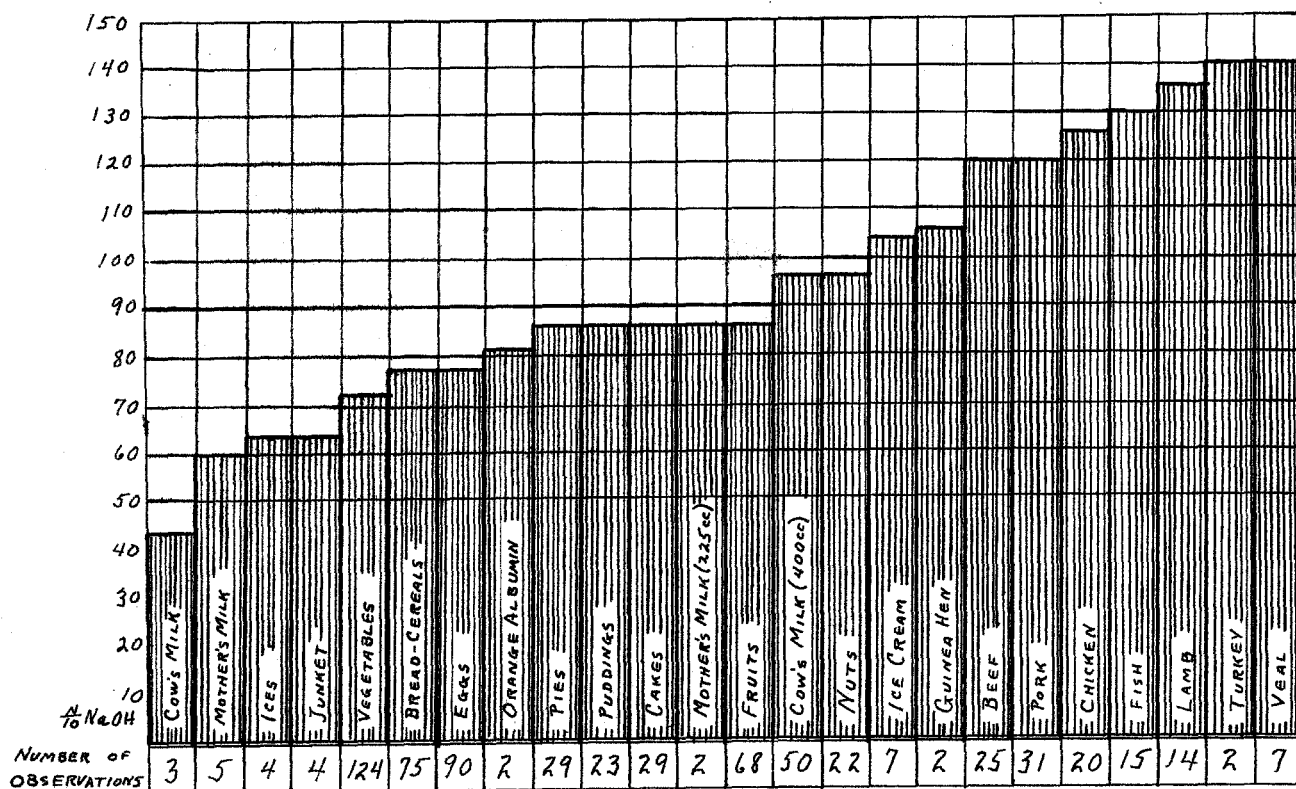


Figure 3.

Figure 3 shows the relative acidity produced by the various types of foods, the figures representing the average highest total acidity for each type.

Another important factor in the production of acidity in the stomach is the age of the individual. Bloomfield and Keefer (8) have shown that the acid secretion of the stomach decreases with age. In their investigation, they used the alcohol test meal on a series of individuals who were normal as far as disease of the stomach was concerned. They found that the total acidity may range from 0 to 135 (c.c. of tenth normal sodium hydroxide) and still be

compatible with health and with the absence of demonstrable disease in the stomach. Figure 4 shows the correlation of average total acidity with the age of the individual.

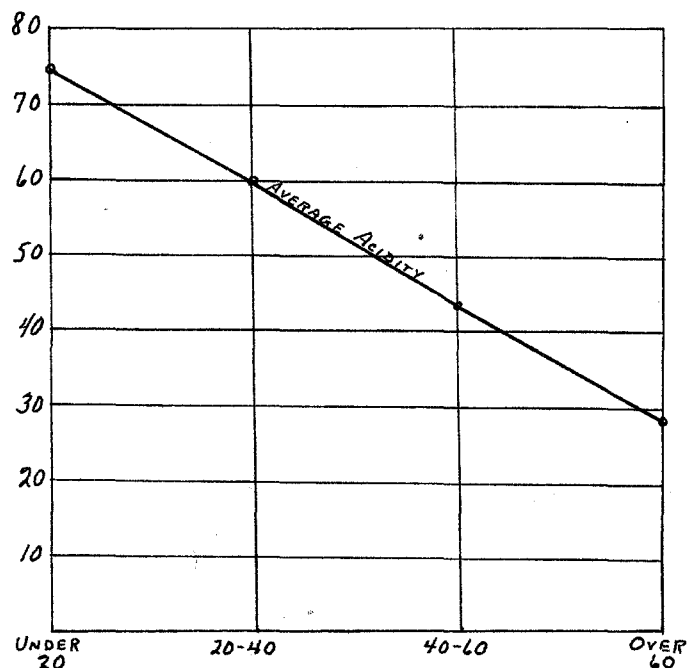


Figure 4.

The same authors further correlated their findings with the general degree of physical fitness of the individual. In this series they excluded desperately ill and moribund patients, dividing them into four groups; good, fair, poor and bad. They found the average total acidity for the "good" and "fair" groups to be 69, while that of the "poor" and "bad" groups was only 33.

They concluded that the values for acidity in the stomach may vary over a wide range but on the whole they could be correlated with two factors; age and physical fitness. The age factor seems to be the more important; as people grow older they produce a diminished acid secretion.

Besides these general physiological factors, there are certain diseases which greatly influence the acid secretion of the stomach. These may be diseases of the stomach, diseases of the gastro-intestinal tract, or diseases elsewhere in the body. These factors will be discussed later in detail.

Hydrochloric acid has the power of combining with protein substances taken in as food, thus forming the so-called "combined hydrochloric acid". The term combined hydrochloric acid is a misnomer. When free hydrochloric acid is treated with a protein, the latter functions as a base and a salt is formed. Therefore, instead of having "combined hydrochloric acid" we have a protein salt of hydrochloric acid. The formation of this salt naturally reduces the hydrogen-ion concentration (47).

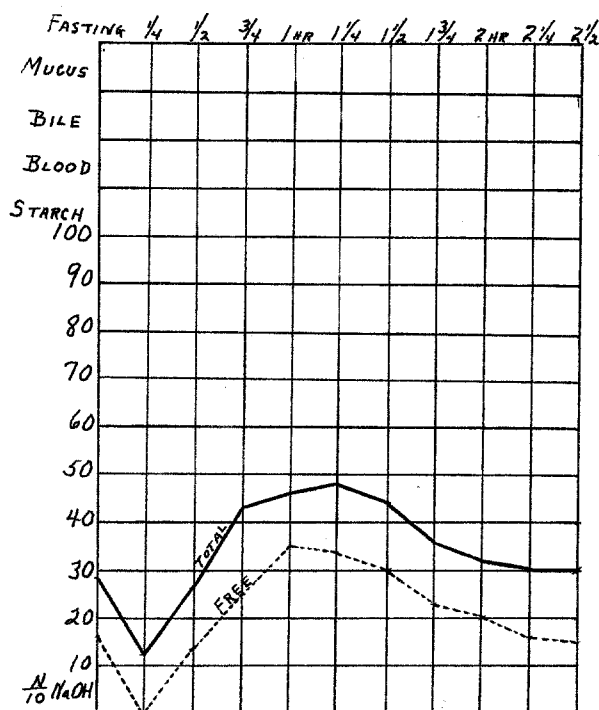


Figure 5.

Bennett (7) shows that the total acidity in normal subjects runs roughly parallel to the free acid curve, reading about ten to twenty points higher. This, however, is never exactly parallel. To show the normal relation between free and total acidity, Bennett has given us a chart of the averages taken from normal curves (Figure 5).

It can be readily seen, then, from the origin of the combined hydrochloric acid that its concentration will be determined by the same factors as determine that of the free acid, as well as the amount and type of protein food present in the stomach. Its significance clinically is very little, except to show, when added to the free acid values, the total output of hydrochloric acid by the secretory glands.

Lactic acid, although it has practically no physiological significance, is of considerable importance clinically. As to the origin of lactic acid, there has been a long controversy as to whether this is secretory or fermentative. It has been mentioned earlier in this paper that Bidder and Schmidt in 1852 definitely proved that hydrochloric acid is the normal acid in the stomach.

Werner (cited in 90) in 1880 pointed out that lactic acid occurred normally in the stomach in the first stages of digestion but if found in the later stages, it constituted a pathological condition. "Lactic acid is not secreted in the stomach, but results from the fermentation of the starch, sugar and protein substances found in the gastric contents. This formation of lactic acid is inhibited in the second stage of digestion by the normal secretion

of hydrochloric acid. If there is insufficient hydrochloric acid, or if the ingest remains too long in the stomach, there is a rapid development of micro-organisms introduced into the stomach by the food. These giving rise to fermentation of fermentable substances of the gastric contents, alcoholic as well as lactic acid fermentation can take place."

In 1885 Ewald noted a prolongation of the lactic acid phase in pathological conditions, particularly in carcinoma of the stomach. In 1892, Boas began to write on this subject and claimed that lactic acid was a specific indication of carcinoma of the stomach. Later, however, Boas retracted his previous views and concluded that the production of lactic acid was due to stagnation and reduced acidity, factors which may be present in other conditions and absent in carcinoma (2).

Even at the present time, however, there are still some who adhere to the belief that lactic acid is produced by carcinomatous cells in the stomach.

MacLean (69) states that the idea of lactic acid formation arising from the fermentation of stagnation products "is absurd" since he had found lactic acid in large amounts in very early cases of cancer, when the radiologist had reported a rapidly emptying stomach. He further states that even if the stomach is thoroughly lavaged and followed immediately by a test meal, considerable amounts of lactic acid can be found within a half hour.

Moore and Roberts (81) go even further than MacLean in their views. They report that they were unable to find lactic acid in

stomachs apart from cancer, and that its presence had no relation to stasis. "The presence of lactic acid in the stomach contents was pathognomonic of carcinoma of that organ and it probably arose by the specific activity of the cancer cells on glucose."

Dodds and Robertson (26 (27) conducted a careful analytical investigation of the question of lactic acid formation. Carefully controlled tests were performed on seventy-four consecutive cases at the Courtland Institute of Biochemistry with uniform conditions maintained throughout. Quantitative as well as qualitative tests were made on specimens of the gastric contents following fractional test meals. First the stomach in each case was thoroughly washed and then tests were made on the resting specimen, followed by tests on the pooled later specimens.

Their conclusions are, from a clinical point of view, that qualitative tests for lactic acid are so easily influenced by so many substances that no reliance can be placed upon them. Thus the use of practical qualitative tests can be of no help in the clinical diagnosis of carcinoma of the stomach. Delicate quantitative tests also failed to demonstrate the presence of lactic acid in all cases of gastric carcinoma. They found that 47% of the non-malignant cases showed the presence of lactic acid in the resting juice and that 36% showed it in the later specimens.

Further results of these series of tests show without doubt that the lactic acid in the stomach results from fermentation, and by the isolation of its zinc salt and examination of its rotation of polarized light, the possibility of the acid being produced by the metabolism of animal cells is absolutely out of the

question.

It was found that the more thorough the lavage of the stomach, the lower the concentration of lactic acid in subsequent tests. Thus Robertson answers MacLean's contention that even after thorough washing of the stomach lactic acid will be produced in a short while and refutes his belief that the lactic acid is produced by the carcinomatous cells.

Although lactic acid is usually present in carcinoma of the stomach, it must be realized that it is not an early sign and when the acid makes its appearance, the growth is usually too far advanced to be amenable to therapeutic measures.

REGULATION OF GASTRIC ACIDITY

The mechanism of the control of gastric acidity has always been an interesting source of speculation. At one time it was thought that the saliva swallowed with the food was an important factor in reducing the acidity of the stomach. Bennett and Ryle (6) mention the neutralization of gastric juice by saliva as a factor in the reduction of acidity. As a matter of fact, if there is any neutralization at all by saliva, it is negligible. Carlson (16) states the titration of alkalinity of the saliva is low (0.8 sodium carbonate). Therefore, if the saliva plays any part at all in the control of acidity, it is by dilution rather than by neutralization.

During the last twenty years, most men have believed that the most important factor in the regulation of gastric acidity is the neutralization of the gastric contents by duodenal regurgitation. Boldyreff (12) in 1914, was the first to advance this idea of self

regulation of gastric acidity by regurgitation of the alkaline duodenal contents. According to his theory, the initial high acidity of the gastric juice (about 0.5% hydrochloric acid) is rapidly lowered to an optimum level which oscillates between 0.15 to 0.2% hydrochloric acid by a reflex ^{Lu} into the stomach of alkaline juice from the duodenum. He believed the pancreatic juice to be the most important factor in this process of neutralization.

Boldyreff also found that in cutting off the secretions from the duodenum, the stomach, then left to its own resources was not able to lessen the acidity of its contents. He believed that bile, saliva and the alkaline gastric mucus played a role but that the important juice in this regulating mechanism was the pancreatic secretion.

Spencer, Meyer, Rehfuess and Hawk (96), by means of delicate tests indicating the presence of trypsin in the stomach contents and correlating its concentration with the degree of acidity, were able to confirm Boldyreff's work. They found that the value for trypsin was high in the presence of low acidity or alkaline reaction and of low value when the gastric contents were of high acid concentration. They further demonstrated that a fall in acidity is usually accompanied by a rise in the trypsin value. Their belief is that the regurgitation of the duodenal contents into the stomach plays the role of automatic regulation of high acidity. They further believe it is one of the protective functions of the body and has for its purpose the protection of the small bowel against irritants.

Carlson has confirmed this work to his own satisfaction and he has given a clinical interpretation of the mechanism (16). "This mechanism probably breaks down in cases of so-called hyperacidity in man. In cases of hypersecretion, the quantity of gastric juice secreted is greater than normal, but the neutralizing factors are about the same as those in a normal stomach. Thus it is a balance between the secretion rate and the neutralization capacity. Impairment of the neutralization factors, or an excessive secretion rate, or pyloric obstruction would tend to render the acidity of the gastric content equal to that of pure gastric juice; in other words produce clinical 'hyperacidity'."

In 1922, Bolton and Goodhart (13) studied this point by making complete chloride determinations, proving that when the acidity of the stomach reached a certain average height, regurgitation of the duodenal contents occurs and brings down the acidity curve by neutralization. They attach so much importance to the neutralizing process that they say, "This neutralization cannot be left out of account because it normally regulates the acidity of the stomach contents and in morbid processes this self-regulating mechanism is interfered with by definite causes with the production of well-defined results." According to Bolton it is the chief factor in modifying the curves of acidity.

The conclusions deduced by the work of Bolton and Goodhart are worth considering.

- "1. Duodenal regurgitation occurs at a definite period but not always at the same time during the digestive cycle,

and must be considered as a definite link in the chain of events in the digesting stomach.

2. It determines the shape of the curves of hydrochloric acid and the inorganic chlorides, the former rapidly falling and the latter rising.

3. The absence of free hydrochloric acid or the presence of a low hydrochloric acid curve, are no indications, when taken alone, that gastric secretion is correspondingly diminished, for the total chlorides might still be at a normal height, in which case these findings are due to free duodenal regurgitation.

4. A curve of the climbing type does not necessarily indicate hypersecretion, but rather a delayed and deficient pyloric relaxation.

5. The two great factors contributing to the form of these curves are (a) Varying degrees of pyloric relaxation and duodenal regurgitation, and (b) Hypersecretion.

6. The curve of active hydrochloric acid is no measure of actual gastric secretion. It represents only a balance between these two processes--secretion and neutralization."

Another factor influencing the acidity curve, which has been given more or less importance by various authors, is the alkaline secretion of the pyloric mucosa. Even as early as Pavlov this was recognized to be a factor in lowering the acidity of the gastric contents. Pavlov (84) made the following observation, "Careful investigation of all data leads forcibly to the conclusion that the juice, as it is

poured out by the glands, always possesses the same degree of acidity. After it is secreted by the glands it has to flow over an alkaline mucous membrane and inevitably becomes more or less neutralized, that is to say, its acidity reduced. It is a rule that the acidity of the juice is closely dependent upon its rate of secretion; the more rapid the latter, the more acid the juice, and vice versa."

Baird, Campbell and Hern (1), with continuous suction in the duodenum during fractional analyses, thus excluding regurgitation, found that the stomach curves for acid and for chloride remain as widely separated as in earlier test meals without the duodenal tube. They observed also the same decline in acidity which they obtained without suction. From these observations, they were convinced that no duodenal regurgitation took place, concluding that the stomach contents were often neutralized by the alkaline pyloric secretion and that no duodenal regurgitation was necessary.

Carlson, however, believes this to be a very insignificant factor in the control of acidity (16). He gives the alkalinity of the gastric mucus as only 0.05 to 0.10 per cent. in terms of sodium bicarbonate. According to this it would require 100 to 200 c.c. of mucus to reduce 100 c.c. of gastric juice from the normal acidity of 0.45 per cent. to the optimum of 0.25 by neutralization and dilution.

Carlson (16) introduces another conception as to the control of acidity in the stomach. He suggests that the actual acidity of the juice as secreted may increase with the secretion rate

until the maximum acidity is reached, with the high average rate of secretion under conditions similar to those in the salivary glands, where the concentration of the salts and the organic materials increases with the rate of salivary secretion. If this is true, the gastric juice secreted at a low rate should show a lower osmotic concentration and a smaller total of chlorides than the juice secreted at a high rate. According to Carlson, the figures reported by Umber for man and by Roseman for the dog support this view.

MacLean and Griffiths disagree with Boldyreff and others who believe duodenal regurgitation to be an important factor in the regulation of acidity (70). They have endeavored to show that the fall in acidity which occurs toward the end of normal gastric activity cannot be explained adequately on the basis of duodenal regurgitation. They found that this reduction in acidity occurs without any evidence of the simultaneous appearance of trypsin and carbon dioxide, which one would expect to find if a reflex of duodenal fluid had taken place.

When mineral acid was introduced into the stomach, they observed the acidity of the contents subsequently fell. This led them to believe that the acidity of the fluid introduced is lowered by the secretion of a neutral fluid containing neutral chloride. They consider that a similar process occurs in the later stages of digestion, when the concentration of acid normally diminishes.

"There is evidence that (a) the gastric glands can secrete sodium chloride, and (b) that the concentration of this salt undergoes change. Since, as we have shown, duodenal regurgitation is

not a prime factor in the regulation of gastric acidity, we have put forward evidence for the view that the chloride ion brought to the glands by the blood as sodium chloride is secreted at a definite fixed concentration, part of it unchanged as sodium chloride and part of it changed into hydrochloric acid, and that the extent of this change governs the acidity of the secreted juice. Thus during the early stages of digestion, when the acidity of the gastric contents is rising, there is a marked change of sodium chloride into hydrochloric acid so that the neutral chloride curve is low; but when the acidity reaches a certain value, which may be different in different subjects, the degree of transformation of the sodium chloride diminishes until more or less all of this salt is secreted unchanged. This brings about a fall in acidity and a corresponding rise in neutral chloride as shown by gastric analysis curves."

Further investigations were carried out by the same men on dogs with isolated Pavlov pouches (71). Here they obtained the same results that they had observed in man. This they advanced as further proof of their earlier contention: "Since the acid concentration in an isolated pouch into which no regurgitation of alkaline duodenal fluid can possibly take place, shows, during digestion, a reduction of acid and a corresponding increase of sodium chloride in the same manner as found in the normal stomach, it follows that regurgitation is not necessary to bring about the reduced acidity found in the normal stomach during the later stages of digestion. This reduction is brought about by the stomach quite irrespective of any regurgitation that may take place."

Later work by MacLean and Griffiths (72) showed that the stomach rapidly reduced the acidity after various acids were injected into the normal stomach. "The concentration of the hydrochloric acid in the normal stomach is automatically regulated by the hydrogen-ion concentration of the gastric juice. The presence of a certain concentration of acid in the stomach inhibits secretion of acid, with the result that a neutral fluid containing chloride is secreted, which by dilution reduces the acidity of the gastric contents".

McCann (73), in 1929, performed a series of interesting and significant experiments on dogs, investigating the question of acid regulation in the stomach. He divided his studies into two series. In the first, he instituted surgical duodenal drainage, thus shunting all duodenal juices into the lower ileum to eliminate duodenal regurgitation. In the second series, he performed complete and partial resections of the pyloric antrum of the stomach.

In his first series he found, after all duodenal alkalis were shunted away from the pylorus, that there was no change in acidity or chloride curves from the results obtained pre-operatively. This is definite proof that duodenal regurgitation is not the essential mechanism for controlling the acidity of the gastric juice, although it may be an associated phenomenon.

In his second series, he found that the integrity of the prepyloric segment is essential for the normal control of acid secretion. After resection of this region, he found there was a very slow secretion of acid after both a meat and water meal and after

histamine injection. These results indicated the importance of the prepyloric segment in determining the acidity of the juice in the normal stomach, not because of its alkaline secretion, but because it is a significant link in regulating the rate of secretion of acid. This would have a very definite clinical significance in surgical procedures done on the stomach.

GASTRIC ACIDITY IN DISEASE

In the consideration of the acidity curve in disease conditions we must always bear in mind the factors which may influence the curve and be familiar with the mechanisms which produce either a high or low acid response.

For the most part, the gastric secretion gives us a picture of what transpires in the mucosa of the stomach, although as we have noted before, there are other factors influencing this secretion. This includes not only the glandular secreting structures of the mucous membrane but also the intactness of the nerve mechanism, the nature of the stimuli which reach the gland system and the quality of the blood which supplies this area.

The first consideration then, is the quality of the mucous membrane and the nature of the nerve and circulatory factors connected with it.

A diseased mucous membrane should react differently from a normal one and we would expect a change in the secretory output. Disease may produce congestion, inflammation, erosion, ulceration, degeneration, or destruction by malignant growths. Obviously,

the effects may vary. Inflammation may vary from a mild to a severe process causing a complete arrest of the secretory work. Then, too, the extent of the disease condition may vary from a small circumscribed area to an extensive process involving the entire stomach lining. Therefore, we may obtain different responses depending upon the nature and degree of the damage to the mucosa.

The nervous mechanism concerned with the secretory function of the mucous membrane consists of the vagus, the sympathetics, and the local plexuses of Meissner and Auerbach. It is generally believed now that the vagus is an excitosecretory nerve while the branches of the sympathetic are inhibitory (89). A stimulation of the vagus would give a hypersecretion with hyperacidity while an inhibition would bring about the reverse. A stimulation of the sympathetic would also bring about an inhibition of secretion. With the close association between the endocrines and the autonomic nervous system, any endocrine disturbance may show its effect upon the gastric secretion. The vagus probably carries the psychic and emotional response and is undoubtedly closely associated with the cephalic phase of gastric secretion. Again, the nervous factors are concerned with the reflex disturbances of gastric secretion arising from disease in other parts of the abdomen, which is not uncommonly seen.

The quality of the blood supplying the mucous membrane exerts its influence on gastric secretion. Toxins or bacteria in the blood stream may alter the secretion and produce a hypochlorhydria or an achlorhydria.

The degree of duodenal regurgitation, although it is not the only factor in the regulation of acidity, will influence the curve to a certain extent. This must be taken into consideration in the interpretation of the acidity curve for diagnosis of gastric disease.

Carlson (17) attaches a great deal of importance to the rate of evacuation of the stomach in the production of hyperacidity. He states that there is no disease capable of producing true gastric hyperacidity. The causes of hypersecretion, he believes are delayed emptying time from obstruction of the pylorus or gastric stasis. Hyperacidity, then, would be a mechanism of damming back the secretion in the stomach, thus giving a greater acid concentration upon examination.

In the consideration of the mechanism of high acid response, we find that this finding must depend upon one of the following factors:

1. An overstimulation of the mucous membrane, or at least excessive work on the part of the mucosa.
2. Defective regurgitation.
3. An increase in pyloric tension, causing delayed evacuation.
4. The normal response to a certain degree of food-stuffs, namely, most of the proteins.

Excessive work on the part of the mucous membrane can be due to an over-stimulation of the nerve mechanism of the stomach, more particularly the vagus nerve, by any emotional, toxic, bacterial, chemical, or endocrine substance. In the same manner, any of these

substances might inhibit the sympathetic nerve, thus producing the same result by allowing the vagus to overact. It is possible that some toxic substances may reach the mucous membrane by way of the blood stream and by direct irritation produce a hypersecretory response. The mucous membrane, therefore, can be stimulated either through its nerve mechanism or through its circulation.

There is a group of cases in which we have an actual hypertrophy of the glandular elements of the mucous membrane, or a true hypertrophic gastritis which will produce large amounts of acid secretion (89).

Rehfuss (89) considers defective duodenal regurgitation to be the most important cause of pathological hyperacidity. An increase in the tension of the pylorus, will give high acid readings on examination. This is obviously related to duodenal regurgitation.

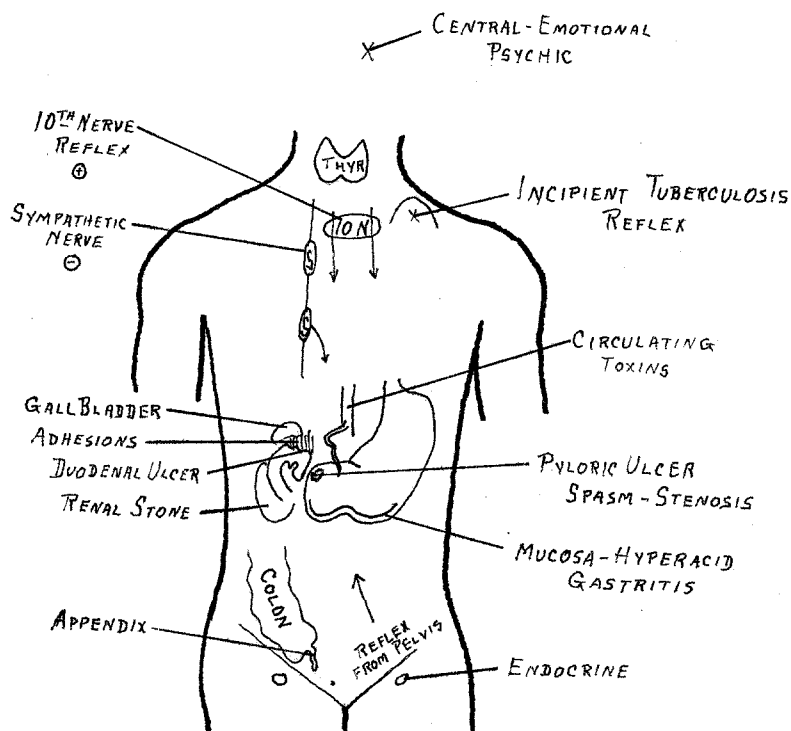


Figure 6. Causes of hyperacidity.

Figure 6, taken from Rehfuess (89) shows some of the causes of hyperacidity.

On the other hand, low acidity may be due to:

1. A deficiency in the work of the mucous membrane.
2. An excessive regurgitation from the duodenum.
3. A disturbance in the rate of secretion.
4. A low normal response to certain foods.

In the production of hyperacidity due to mucosal alterations, we are dealing primarily with a functional mechanism involving an intact mucosa. In low acidity, we are dealing in many cases, not with a functional upset, but with actual organic changes in the mucous membrane of the stomach. In most cases of inflammation there is actual damage to the glandular elements which may go so far as to produce permanent atrophy or degeneration. In other cases, however,

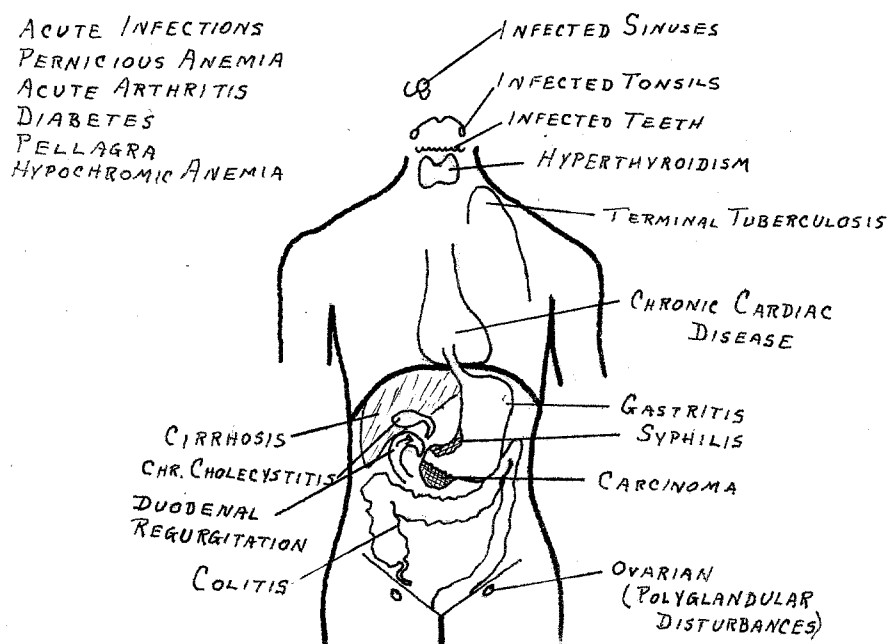


Figure 7. Causes of anacidity and subacidity.

we have a functional change here too, as seen in many toxemias, acute infections, chronic kidney disease, etc., in which, after the primary condition is corrected, we have a return to normal acidity.

Figure 7, taken from Rehfuess (89) shows some causes of anacidity and subacidity.

GASTRITIS

In the consideration of gastric acidity in specific diseases, it might be well to begin with gastritis, in which the pathological process involves the mucous membrane itself. In this discussion, I will not differentiate between acute and chronic forms except to say that, so far as we are concerned with acidity findings, the difference is one chiefly of duration, with the resulting pathological changes that take place in any inflammatory condition as it passes from the acute to the chronic stage.

To understand the physiological changes in the stomach due to gastritis, it is necessary to know the histopathological changes that occur in the mucous membrane. Hayem (cited in 89) describes an early hypertrophy and later degeneration of the chief cells with a progressive degeneration of the parietal cells. In most cases there is a progressive connective tissue invasion with a mucous transformation or atrophy of the glandular elements. In other words, the tendency in gastritis is toward a progressive lessening in secretory work, although in the beginning there may be a tendency to irritation and excess.

Rehfuess (89) states that one finds a falling off in free acidity

and usually an increase in combined acidity with every variation from the subacid cycle, delayed digestive cycle, to anacidity and total achylia, which one would logically expect to find in an atrophy. According to Rehfuess it is possible by the study of the acidity curve to estimate accurately the extent of the damage done to the mucosa by the pathological process.

Even as early as Beaumont, it was noted that gastritis can lead to a cessation of secretion (3, 4). Some men go as far as to say that the cause of all achlorhydric conditions is due to gastritis. This will be discussed later with the consideration of achlorhydria and achylia.

As to the etiology of gastritis, there are a multitude of causes for this condition which may be grouped under four main heads, gastritis by ingestion, toxic gastritis, infectious gastritis, and secondary gastritis. No matter what the cause, we may still obtain all variations of subacidity according to the severity and extent of the lesion.

PEPTIC ULCER

The most common lesion associated with hyperacidity is peptic ulcer. The etiology of peptic ulcer was long thought to be due to hyperacidity. Within recent years, many facts have shown that while the gastric secretion is not the cause of the production of ulcer, it can be the chief contributing agent in its extension and chronicity (89). Sippy (95) believes that peptic ulcer develops in approximately the following manner: a circumscribed area of the mucosa or wall of the stomach or adjacent duodenum, through

malnutrition or necrosis, loses its normal resistance to the peptic action of the gastric juice and becomes digested. The resulting defect is an ulcer. He states that elsewhere in the body such local defects undergo repair while in the stomach and duodenum, they do not, because the granulating surfaces are subjected to the action of the digestive juice. It was to inactivate peptic activity and give nature a chance to heal the lesion that the alkaline treatment bearing Sippy's name was begun.

Hurst (53) believes there is an inborn tendency or constitutional predisposition to hyperacidity which he describes as a hypersthenic gastric diathesis. This he believes is one of the contributing factors in the etiology of peptic ulcer.

In the examination of the acidity curves, we find that duodenal ulcer gives a more uniform response than does gastric ulcer. Eggleston (31) believes there is less apt to be disturbances in motility incident to pyloric malfunction in gastric than duodenal ulcers. The greater frequency of hyperchlorhydria in the latter he would explain on the basis of disturbed motility. This is directly in accord with Carlson's belief that hypersecretion is due to gastric stasis or pyloric stenosis. Eggleston further states that if those cases with delayed emptying time are excluded there is practically no greater percentage of hyperchlorhydria than in a similar number of normal persons.

In Moynihan's (33) series of 39 cases of gastric ulcer and 71 cases of duodenal ulcer, he found that 20 per cent. of his gastric ulcers gave an increased acidity while 72 per cent. of his duodenal ulcers gave higher than normal readings. On the other hand, he

found delayed emptying time in 78 per cent. of his gastric ulcers and in 72 per cent. of his duodenal series. This would indicate that disturbed motility is not the explanation of the disparity between gastric and duodenal ulcer curves.

Hunter (51) made an investigation of 174 cases of gastrointestinal disorders in which the diagnosis was confirmed by operation or autopsy. In the analysis of fifteen cases of chronic ulcer of the duodenum, 88 per cent. showed curves considerably above normal. In every uncomplicated case there was rapid emptying time, the curve showing an abrupt rise with a high plateau. Where the condition was accompanied by stenosis the emptying time was delayed and the curves showed a gradual climb to a high level. This, again, would indicate that disturbance of motility is not the great factor in producing high acidity in duodenal ulcer.

Hurst (56), in the study of 16 cases of gastric ulcer and 32 of duodenal ulcer, found an associated gastritis, which he believes accounted for low acidity findings. After treatment for the gastritis he repeated gastric analyses on those patients and found that the acidity had increased in all but eight cases, these eight cases having had a high acidity even before the treatment was begun. After this treatment, all 48 cases had high acid ranges. He concludes, then, that if all ulcer cases were given treatment for gastritis and then re-examined, the proportion of high acid curves would approach 100 per cent.

I would conclude from these observations that hyperchlorhydria is associated with both gastric and duodenal ulcer and those cases which show a normal or decreased acidity have an associated gastritis.

The fact that hyperacidity is found more consistently with duodenal than gastric ulcer can be explained by the greater tendency for a gastric lesion to be associated with an inflammatory process involving the mucosa of the stomach.

It is true that an ulcer complicated with a pyloric stenosis gives a different acidity curve than the uncomplicated case, although it does not follow that the delayed emptying of the stomach is the main cause for the hyperacidity. Hunter (51) in describing hyperacidity curves in ulcer, gives the typical curve for uncomplicated ulcer, both duodenal and gastric, as having an abrupt rise, with either a high plateau or drop to the base line. Cases complicated with pyloric stenosis or pylorospasm show a more gradual climb to a high level. Rehfuss (89) describes the typical uncomplicated ulcer curve with a larval hyperacidity which is an abrupt rise to a high level. In the cases with stasis, Rehfuss, too, describes the typical curve as having a slow gradual climb or tardive hyperacidity.

CARCINOMA OF THE STOMACH

It has long been known that carcinoma of the stomach is usually associated with absence of free acid in the gastric juice. Van den Velden (cited in 9), in 1879, was the first to make studies of the gastric secretion in patients who had cancer of the stomach. He found that patients with gastric cancer showed no free acid in the stomach contents. More recently, however, it has been noted that free acid may frequently occur with gastric cancer. The percentage of cases of cancer showing achlorhydria varies with different

observers. Brown (15) states that in more than 75 per cent. of cases, free hydrochloric acid is absent while Hurst (57) found anacidity in 65 per cent. of cases. These figures were derived without the use of histamine. In a series of 56 cases of proved carcinoma of the stomach, Bloomfield (9) reports anacidity in 69 per cent. even after histamine injection. In those cases in which acid was present, it was usually greatly diminished.

There have been many explanations advanced for the defective secretion in carcinoma of the stomach. Among them are:

1. Neutralization of gastric juice by duodenal contents.
2. Suppression of gastric secretion by mucus.
3. Injury of the acid-bearing glands of the pylorus by the tumor.
4. Interference with gastric nerves by the growth.
5. Neutralization of gastric juice by alkaline products of the malignancy.
6. Chloride starvation.
7. Gastritis associated with the lesion.

Pollard and Bloomfield (86) in their study of this question have shown that it is impossible to adequately explain the acid changes on the basis of any one of the above suppositions except the last. The view that gastritis is responsible for these acidity changes has been the one most widely held.

It had been thought by most men, however, that the gastritis was a result of the growth itself and that this was a progressive affair, secretory activity diminishing as the condition progressed.

Rehfuss (89) believes that achlorhydria is a late manifestation of cancer and that acid, both free and total, is present in the early stages of the disease. He states that "gastric cancer tends to produce a progressive downward trend in the secretory output."

More recent work, however, tends to show that gastritis, instead of being the result of the growth, precedes this condition and is even a pre-disposing factor in the development of carcinoma. Konjetzny and Saltzman (cited in 86) in 1913 produced very positive evidence by demonstrating histologically transitions from gastritis to actual cancer. Hurst (55) has strongly supported this view on clinical grounds. He believes that when free acid is present, the carcinoma is secondary to ulcer and when achlorhydria exists it is generally secondary to gastritis. He states that achlorhydria, then, is not a sign of advanced carcinoma in the early stages of which free acid is present. The duration of symptoms would tend to be considerably shorter in cases where free acid is present than in cases of achlorhydria, whereas the reverse is actually the case. Hurst mentions a case in which achlorhydria was found to be present many years before the appearance of the symptoms of cancer.

Eggleston (30) believes the achlorhydria found in gastric carcinoma to be secondary to an atrophic gastritis, which is an etiological factor in malignant conditions. Bloomfield and Pollard (9) in their analysis of the question, strongly support the view that achlorhydria and gastritis precede the malignant change in the stomach. They point out that there is no documentary evidence in literature to show that secretion diminishes as the growth progresses

and there is no correlation between the extent of the tumor and secretion.

As to the occurrence of free hydrochloric acid in some cases of carcinoma, it is now believed by a number of authors that this condition can be explained on the basis of carcinoma developing from chronic ulcer of the stomach. Miller (80) states that two-thirds of carcinomata follow chronic gastritis, the other third resulting from ulcer.

Bloomfield has made a recent investigation of this matter (10). In 92 cases of carcinoma of the stomach, 76 per cent. showed a true anacidity with histamine, while 24 per cent. showed some free hydrochloric acid. In those that showed acid he found they were not grouped at the anacidity end of the scale as one would expect, but covered the entire range of normal secretion. In fact, there were only six cases with a total acidity under 60, but there were 15 with an acidity above 60. Such a bimodal distribution curve would suggest that we are dealing with two classes of material. His conclusion was that the carcinomata showing acidity has a different origin from those arising on a basis of gastritis with anacidity.

Following this observation, Bloomfield made an analysis of the twenty-two cases of cancer with acid as to the possibility of antecedent ulcer. His results are shown in the following table:

| | Ca (acid) % | Ca (anacidity) % |
|------------------------------|----------------------------------|--------------------------------------|
| Antecedent ulcer | 68 {definite 41 indefinite 27 | 0 |
| No antecedent ulcer | 9 | 81.5 {definite 45.5 indefinite 36 |
| Relation to ulcer unknown | 23 | 18.5 |

This is strong evidence, then, that in most cases of cancer with preservation of acid, peptic ulcer is the initial event. The practical value of these statistics is that the presence of acid is the crucial factor in the diagnosis of cancer ex ulcere.

SYPHILIS

Gastric syphilis may resemble carcinoma very closely, both as to acidity findings and as to filling defect as seen by X-ray examinations. This may take the form of simple syphilitic gastritis, syphilitic ulcer, gumma and tumor formation, or syphilitic stenosis of the pylorus. In most cases, there is achlorhydria or at least a hypochlorhydria (89). Eusterman (32) has shown in a series of 93 cases of gastric syphilis that 85 per cent. had anacidity. He believes the achlorhydria to be due to a chronic interstitial gastritis because this was uniformly present in cases in which pathological specimens were examined.

In the systemic phase of syphilis, without a localized stomach lesion, we also have a tendency to lowered acidity. Neugebauer (cited in 23) found in the examination of 200 syphilitic recruits from 20 to 25 years of age, that 62 per cent. showed hypo-acidity, 18 per cent. anacidity, and 17 per cent. hyperacidity. He explains the lowered acidity as due to a change in the tonus of the vagus, a direct disease of the mucosa or a combination of these factors. In a study of syphilitic children, Dorne, Brams and Tumpeer (28) found the same tendency to lowered acidity.

In tabes with gastric crises, however, a different picture is found. Most authors believe that hyperacidity is associated with

gastric crises of tabes although Rehfuss (89) believes that low acid values are almost as frequent. Ryle (91), however, describes the curve as seen between crises as a steep climbing curve reaching a high level, which is suggestive of pyloric hypertonus. Ryle further states that during the crisis, X-rays show the stomach to be in a state of hypertonus. Immerman (60) agrees with Rehfuss and states that hyperacidity or excess amounts of acid are not always found in tabes, although it is a common finding.

PERNICIOUS ANEMIA

One of the most interesting conditions associated with changes in gastric acidity is pernicious anemia. With this, the acidity changes are the most constant of all conditions associated with alterations of gastric secretion. Fenwick (37) (38), in 1870, first described the absence of hydrochloric acid in pernicious anemia. In his work he noticed that patients who had died of pernicious anemia showed both an achlorhydria and an atrophy of the secreting glands of the stomach. From these observations he made the suggestion that pernicious anemia probably arises from an atrophy or paralysis of the stomach.

Levine and Ladd (64) found that anacidity was so constant in their series of 143 cases that the presence of free acid should make one seriously question the diagnosis of pernicious anemia. Later studies by Bloomfield and Pollard (9) give the same results even with the use of such a powerful stimulant as histamine.

The etiology of pernicious anemia as suggested by Fenwick was not generally accepted at the time it was advanced, but instead

work was directed toward the adrenals, the bone marrow, and other hemopoietic organs in search for the cause of this condition. In recent years, Hurst (57) revived the old idea of a primary gastrointestinal defect.

Castle (18)(19)(20) and his associates have made the greatest advance in this disease since the discovery of liver therapy by Minot. In a series of experiments they have shown that beef which has been ingested or incubated with the fasting stomach content of a healthy individual will give a response in the red blood cell formation if ingested later by a pernicious anemia patient. Neither beef or normal gastric juice will produce this effect alone.

By this work they have proved that, in cases of achlorhydria or achylia, a primary anemia develops secondary to an imperfect digestion of the proteins. They further show that this lack of protein digestion is not due to the absence of free hydrochloric acid, nor is it due to the absence of pepsin or both, as many cases exhibiting an achlorhydria with an absence of pepsin fail to show any anemia whatever. Their conclusions are that it is due to the lack of an intrinsic substance secreted by the normal gastric mucous membrane which interacts with some extrinsic factor in beef muscle to form a hemopoietic substance. This substance is capable, in the presence of a normal diet, of promptly relieving the anemia of a patient suffering from pernicious anemia. As further argument, they report several cases of total and sub-total gastrectomy causing a condition similar to pernicious anemia.

Morris and his associates (82) have isolated a specific

hemopoietic hormone by concentrating normal gastric juice. This they have called addisin in honor of the man who first described pernicious anemia.

Another argument which has been advanced in favor of deficient gastric secretion as an etiological factor in pernicious anemia is the fact that anacidity may precede by many years the appearance of other features of pernicious anemia. Hurst (57) cites several cases in which achlorhydria preceded pernicious anemia by varying lengths of time. Connor (22) in his discussion of the hereditary factor of pernicious anemia cites a large number of observations in which achlorhydria preceded anemia from four to twenty-five years. Davis and Vanderhoof (24) report the development of pernicious anemia in a case while under their observation. This case showed achlorhydria from the beginning.

Davies (23) summarizes very well the current trend of thought as to the etiology of pernicious anemia. "That achlorhydria, or rather the gastric lesion indicated by achlorhydria, found in pernicious anemia is the underlying cause for the development of the malady is now gaining acceptance and among the reasons for this view may be mentioned--the finding of achlorhydria years before the presence of anemia, the constancy of the achlorhydria even after restoration of complete health by means of liver administration, and lastly the important observations of Castle. Indeed the view of Fenwick that the achlorhydria is only an index of the gastric atrophy and the anemia the sequel of such atrophy has been confirmed by these most recent observations."

Associated with pernicious anemia is often seen a neurological condition known as combined sclerosis or sub-acute degeneration of the cord. In many cases combined sclerosis may occur without the presence of anemia and often is seen in other conditions associated with achlorhydria such as carcinoma of the stomach, tuberculosis, etc. (99). In many cases it is known to precede pernicious anemia but still associated with achlorhydria. Hurst (54) cites 11 cases of typical sub-acute degeneration of the cord in which all showed a complete achlorhydria. In one case the achlorhydria was found to exist a year before the first signs of cord involvement. Digestive symptoms in combined sclerosis are as common when the nervous symptoms precede the anemia as when the reverse is true, which would indicate some definite relationship to achlorhydria and gastric function.

IDIOPATHIC HYPOCHROMIC ANEMIA

In the last few years there has been a great deal of work done on hypochromic anemia. Faber (cited in 9) seems to have been the first to study the question of anacidity in anemias other than pernicious anemia. He found in a series of 185 anemia cases, other than pernicious anemia, which showed anacidity that there were 37 with a hemoglobin below 65 per cent. In a later work (34) he noted a low color index and small cell diameter in anemias of this type. This condition soon came to be recognized as a separate disease entity under the designation of several different names, the best of which is "idiopathic hypochromic anemia".

Witts (102) made a very careful study of this condition in 1930.

In his analysis of 38 cases of unexplained secondary anemia at Guy's Hospital, he found 30 cases of achlorhydria. On re-check he found causes to explain the anemia in the eight who showed free hydrochloric acid. He concluded that the cardinal symptom of this condition was achlorhydria and that achlorhydria was the primary etiological factor in the disease. He also noted that it was closely connected with pernicious anemia in pathology and in familial incidence.

Waugh (98) also found a complete lack of hydrochloric acid in his cases of hypochromic anemia. He believes that achlorhydria, or at least extreme hypochlorhydria, as in pernicious anemia, is a pathognomonic sign of this condition and that all cases that do not present it are not to be included in this group. Waugh believes that in this type of anemia, as in pernicious anemia, we are dealing with a deficiency in gastric activity. This, he says, leads to the absence of some chemical substance which, differing from that of pernicious anemia, is essential for the maintenance of normal hemopoiesis. This substance has to do with hemoglobin formation.

Heath (48), too, believes idiopathic hypochromic anemia to be due to a deficiency of gastric origin in which iron given in adequate amounts leads to alleviation. He believes the achlorhydria to be an indication of a degeneration of the gastric mucosa which is in a way hereditary, in the sense that arteriosclerosis or diabetes is hereditary. This would be indicated because of the occurrence of this condition in families, just

as we see a familial incidence in pernicious anemia.

Probably the best piece of work which has been written on this subject is that of Wintrobe and Beebe (101) in 1933. These authors state that achlorhydria, although usually present, is not as consistent a sign as in pernicious anemia. In classifying their own cases they found:

1. Achlorhydria, even with histamine - 60% of cases.
2. Achlorhydria with Ewald meal, low or normal hydrochloric acid with histamine - 23% of cases.
3. Hypochlorhydria with Ewald meal - 8.5% of cases
4. Normal acidity - 8.5% of cases.

Wintrobe, too believes that defective gastric secretion is the main etiological factor in the production of hypochromic anemia. Just as in pernicious anemia, achlorhydria has been found to precede the development of idiopathic hypochromic anemia. Achlorhydria was demonstrated in 18 per cent. of Meulengracht's (cited in 101) cases some time before these patients came under his observation. In nine of these cases the gastric defect had been found five to twenty years before, at which time no anemia had been observed. Achlorhydria seems to be the one abnormality which persists in spite of successful treatment of the anemia.

Wintrobe and Beebe state: "That defective gastric secretion, usually of many years duration, is the fundamental cause in the development of pernicious anemia is now generally accepted even though the etiologic factors in the production of this disturbance are not known. It is argued that in idiopathic hypochromic anemia

defective gastric secretion is likewise the essential derangement. What has been said about its relationship to pernicious anemia and the available information concerning the incidence of achlorhydria in idiopathic hypochromic anemia lends support to such an hypothesis."

This theory finds support from another angle. An extraordinary feature of hypochromic anemia is the large amount of iron needed in treatment. Wintrobe's patients received on the average of 1.8 grams of iron a day. The daily increment in hemoglobin was only 0.06 grams, which in comparison was very small. This discrepancy between the amount of iron given and the quantity of hemoglobin formed is due largely to defective absorption of iron from the gastro-intestinal tract. This is further suggested by the fact that a dose of metallic iron given parenterally is thirty times as potent as that given orally (101).

Again we have further reason to suppose that defective gastric secretion has an etiological role by the number of instances in which hypochromic anemia has followed extensive gastric operations. Gordon-Taylor and associates (42) report a re-examination of 52 patients several years after gastrectomy. In these cases anemia was found in 23, two of which showed a color index above 1.0, whereas in 11 it was between 0.6 and 0.3. No cause for this anemia was found, but, just as in idiopathic hypochromic anemia, there was evidence of disturbance of gastric secretion. Free hydrochloric acid was found in only three of the patients suffering from anemia.

MISCELLANEOUS

Changes in gastric acidity are seen in a great number of other

conditions but these are mostly due to a reflex mechanism or a direct effect by toxins, chemical substances, bacteria and endocrine elements brought into contact with the gastric mucosa by the blood supply. In most of these there is no pathological change in the stomach and can be classified as functional disturbances resulting from disease in other parts of the body, although in a few cases it is possible that some secondary gastritis may take place. These secretory alterations have practically no diagnostic value, they are usually not constant and changes of any type may occur in the same condition, but it is well to bear in mind that such changes do occur with other conditions in arriving at a diagnosis of patients giving digestive symptoms.

Disease of the gall-bladder frequently causes disturbances in gastric secretion. This change may be in either direction, a hyperacidity or a reduced acidity. Immerman (60) states that in gall-bladder disease, one-third will give normal curves, one-third subacidity and one-third hyperacidity. Hunter in his analysis (51) found in cases with gall-stones, some associated with acute cholecystitis and others with chronic cholecystitis, that 83 per cent. fell within normal limits. With obstruction of the common bile-duct, however, he found very high curves in 88 per cent. of cases. Hunter also found in the examination of chronic appendicitis cases that 78 per cent. of these fell within normal limits.

There has been some interesting work done in connection with

gastric acidity in thyroid disease. Hardt (45) first performed experiments showing the depression of gastric acidity in feeding dessicated thyroid to dogs, thus producing an artificial hyperthyroidism. These experiments were confirmed and proved more definitely by Truesdale in 1926 (97). Chang and Sloan (21) extended the work of Hardt and Truesdale and made observations on the gastric juice of thyroidectomized dogs. With this experimental hypothyroid condition, they noted an increase in the acidity and the quantity of gastric juice.

Wilkinson (100) worked on this question from clinical observations. In 100 cases of hyperthyroidism he found 36 per cent. showed achlorhydria and the average acid of all cases was reduced to slightly more than one-half the normal. He observed that the incidence of achlorhydria in hyperthyroidism rises in proportion to the duration of the toxicity rather than the degree of toxicity. Wilkinson makes the suggestion that depression of gastric acidity is a phenomenon of extreme sympathetic over-stimulation.

There is some argument as to the effect of hypothyroidism on gastric acidity. Katz (61), Levy (85), and Hutton (59), all concur in stating that low thyroid function produces hyperchlorhydria. On the other hand, Lockwood (68) found achlorhydria in 60 per cent. of 10 cases of myxedema. Lerman and Means (63) found 9 cases of achlorhydria in 17 cases of hypothyroidism. In Wilkinson's series (100), 5 cases of myxedema showed an average free acid of 67.5 and a total acid of 81. In four postoperative hypothyroids, the acidity was even higher. One of these patients had had an achlorhydria

before operation.

Bowen (14), in 1926, made fractional gastric analyses on 69 diabetic patients. A complete absence of free acid was found in 29 per cent. Of the patients who had achlorhydria, the average duration of the disease was 6.5 years and the diabetes was severe in every case at time of observation. The duration in the group with normal acid was 2.8 years, while the sub-acidity group was 3.6 years. There was no essential difference in average age in the three groups. Bowen concludes, then, that achlorhydria may be the result of long standing or severe diabetes.

In diseases of the lower intestinal tract, we may obtain acidity changes in the stomach by reflex action. Van Noorden (cited in 60) mentions constipation as an important cause of hypersecretion in the stomach. Immerman (60) states that colitis will cause hyperacidity. On the other hand, Farrell (36) found that artificial colitis in dogs resulted in a reduced acidity. The gastric juice was retarded and lower values were obtained for both free and total acid. The more severe the colitis, the greater reduction was noted in the acidity values.

Even in skin diseases we may find alterations of the stomach secretions. Philpott (85) has noted an association between the various types of eczema and alterations in the gastric secretions. This association has a direct bearing on the skin condition as shown by the fact that correction of gastric dysfunction in the majority of cases is followed by clinical improvement of the eczema. Philpott selected 50 cases at random and tabulated the

acidity findings. He found that 48 per cent. showed a hypoacidity and 44 per cent. showed hyperacidity.

Many cases of secondary anemia, other than hypochromic anemia, show a definite decrease in gastric acidity. Fouts (40) in the examination of the gastric contents of patients having secondary anemia demonstrated that the majority of them show a reduced acidity. The degree of anemia had some influence on this reduction. Anemias of pregnancy, abortions, and miscarriage, had acid values lower than normal, although not as marked as those in hypochromic anemia.

Immerman (60) mentions the abuse of tea or coffee, tobacco and alcohol should not be overlooked as a cause of hyperacidity.

In addition to the conditions mentioned there are a host of other conditions throughout the body which may alter the secretory function of the stomach by reflex action. These alterations are usually more or less temporary, lasting only as long as the original source of irritation remains. A decreased secretion may be a manifestation of cachectic states in a number of different conditions. Acute debilitating diseases, toxic states, all have their effect upon acidity curves. Neurotic tendencies have an important influence and may cause either an increase or a decrease in gastric secretion.

Bell (5) has tabulated the tendency of the acidity curve in a number of diseases. His figures are based on 425 consecutive fractional analyses and are classified according to the position of the curves in Bennet and Ryle's normal charts. His classification is as follows:

- I. Achlorhydria, in which free hydrochloric acid is present in no period of the analysis.
- II. Hypochlorhydria, in which the curve has not exceeded the 10-unit line.
- III. Low normal, in which the curve follows the lower limit of the 80 per cent. normal area of Bennett and Ryle.
- IV. Normal, corresponding to the central zone in which Bennett and Ryle found 50 per cent. of the curves of normal people.
- V. High normal, in which the curves approximated to the upper limits of the 80 per cent. normal area.
- VI. Hyperchlorhydria, in none of which were the free hydrochloric acid lower than 60 units at one or more periods of the analysis.

Figure 8 is the table of Bell's findings.

| DISEASE | Number of Cases | PERCENTAGE | | | | | |
|-----------------------------|-----------------------|-------------------|---------------------------|---------------|--------|----------------|----------------------------|
| | | Achlor- hydria | Hypo- chlor- hydria | Low Normal | Normal | High Normal | Hyper- chlor- hydria |
| Normal (Bennett and Ryle) | 100 | 4.0 | 1.0 | 10.0 | 59.0 | 18.0 | 8.0 |
| Chronic Gastritis | 11 | 45.4 | 18.1 | 9.0 | 0. | 18.1 | 9.0 |
| Gastric Ulcer | 24 | 4.1 | 12.5 | 16.6 | 20.8 | 25.0 | 20.8 |
| Carcinoma of stomach | 10 | 30.0 | 30.0 | 20.0 | 10.0 | 10.0 | 0. |
| Duodenal ulcer | 34 | 0. | 0. | 11.7 | 8.8 | 26.4 | 53. |
| Nervous dyspepsia | 37 | 5.4 | 10.9 | 8.1 | 27.0 | 8.1 | 40.5 |
| Gastro-jejunostomy sequelae | 22 | 18.1 | 18.1 | 22.7 | 18.1 | 4.5 | 18.1 |
| Visceroptosis | 19 | 10.5 | 26.3 | 26.3 | 15.7 | 9. | 21.0 |
| Gall-stones | 7 | 14.2 | 0. | 0. | 57.1 | 14.2 | 14.2 |
| Chronic appendicitis | 13 | 23.0 | 0. | 7.6 | 38.4 | 7.6 | 23.1 |
| Pernicious anemia | 6 | 100. | 0. | 0. | 0. | 0. | 0. |
| Tabes dorsalis | 9 | 11.1 | 11.1 | 22.2 | 22.2 | 11.1 | 22.2 |
| Disseminated sclerosis | 8 | 0. | 12.5 | 12.5 | 50.0 | 25.0 | 0. |
| Rheumatoid arthritis | 8 | 37.5 | 12.5 | 12.5 | 0. | 0. | 37.5 |
| Neurasthenia | 20 | 10.0 | 30.0 | 5.0 | 25.0 | 5.0 | 25.0 |
| Psychasthenia | 11 | 9.0 | 18.1 | 9.0 | 45.4 | 18.1 | 0. |

Figure 8.

SIGNIFICANCE OF HYPERACIDITY AND ACHLORHYDRIA

In the consideration of hyperacidity it might be well to define our term, since there is at present some dispute on this question. Hyperacidity, for our purposes, must be defined as an increase in the titratable acidity of the gastric juice over normal. This would exclude the consideration of the question of whether the gastric juice as secreted varies in acidity and Carlson's argument that no pathological process can produce a hyperacid secretion. The definition of the term as I have stated it is sufficient for practical clinical purposes. As we have stated before, hyperacidity is found in a certain percentage of apparently normal individuals, it may result from irritation of the mucous membrane of the stomach and it may be the result of reflex stimulation of the vagus nerve or inhibition of the sympathetics. Hyperacidity may also result from motor disturbances of the stomach.

In viewing the question of hyperacidity from another angle we find that it may be an important factor in the production of disease. Hurst (53) describes what he would call a "hypersthenic gastric diathesis". This, he says, is an inborn variation from normal which manifests itself in hypertonus of the stomach with active peristalsis and rapid evacuation and hyperchlorhydria with hypersecretion. This seems to have some nervous connection and may be also described as a vagotonic type. Hurst believes that the hypersthenic gastric diathesis is an important predisposing factor in the etiology of peptic ulcer.

Simpson (94) in 1934 made some very significant observations on the relationship between hyperchlorhydria and peptic ulcer. He performed

a series of experiments on guinea pigs, in which the concentration of acid both in the resting state and after a meal are very closely similar to those found in man. These experiments showed the high frequency of the development of ulcer following an attack of gastritis in the presence of hyperchlorhydria. The level of hyperchlorhydria was maintained at 0.5 per cent. hydrochloric acid. Higher figures of concentration produce corrosive lesions without aid of gastritis. Gastritis without the presence of hyperchlorhydria did not result in ulcer formation.

Simpson produced evidence to show the astonishing frequency of gastritis in man from a very early age, its production by a wide variety of agents to which the gastric mucosa is exposed from time to time and the steady increase of the incidence of gastritis with advancing age.

He further points out that the incidence of ulcer is almost identical with the incidence of constitutional hyperchlorhydria. Both Hart in Germany and Steward in England found chronic peptic ulcers of the stomach and duodenum or scars of such in nearly 10 per cent. of all necropsies--almost exactly the proportion of hyperchlorhydria in the young adult population as found by Bennett and Ryle. From these observations, Simpson concludes hyperchlorhydria is a highly dangerous condition, in the possibility of additional devitalization of the gastric mucosa by gastritis.

The significance of achlorhydria has been worked out more thoroughly than has hyperacidity. Thirty years ago, Knud Faber

came to the conclusion that achlorhydria is always secondary to gastritis. This has formed the basis for the prevailing idea in regard to the etiology of achlorhydria. Faber (35), in 1926, made the following statement: "I maintain (1) that chronic achylia has an exogenous cause and is produced by external factors acting on the stomach either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyma; (2) that the anatomical picture of gastritis will develop in both cases, and that the gastritis can lead to more or less atrophy of the glands; but that achylia occurs at such an early stage of the gastritis that there is no question of atrophy, to say nothing of anadeny. That achylia, therefore, may be found in combination with anatomically preserved glands and undamaged gland cells, although there is a well-pronounced gastritis."

Because the mucosa of the stomach is affected by various infections and intoxications, thus producing functional changes, he believes gastritis should be considered in the same category as nephritis and hepatitis.

Another line of thought regarding the etiology of achlorhydria and achylia is the factor of heredity. Many authors believe that an inherited constitutional weakness is the main cause of achlorhydria. Hartfall (46) states that test meals carried out on newborn and very young babies show an incidence of achlorhydria sufficiently high to suggest that some inherited factor is present. Further support for this view is found by the tendency of achlorhydria to occur in many members and several generations of one

family. Conner (22) found 25.9 per cent. achlorhydria among 154 blood relatives of patients suffering from pernicious anemia. This constitutional factor becomes of importance when we consider those instances of familial pernicious anemia, simple achlorhydric anemia, and families which show both these diseases and symptomless achlorhydria.

Hurst (58) believes gastritis and constitutional factors to be of equal importance. Without gastritis there is no achlorhydria but gastritis does not produce achlorhydria unless the patient is predisposed by having the hyposthenic gastric constitution. The hyposthenic gastric diathesis of Hurst (54) is the direct antithesis of the hypersthenic diathesis in which the mucous membrane of the stomach, owing to some obscure congenital deficiency, secretes a decreased amount of hydrochloric acid. Hurst believes (58) that gastritis, in the presence of the hypersthenic gastric constitution may lead to duodenal ulcer and to gastric ulcer and the gastric ulcer may become malignant but achlorhydria does not develop. He believes it is the combination of the apparently trivial causes of gastritis with the hyposthenic gastric constitution which leads to achlorhydria and the conjunction of these with the constitutional predisposition to cancer that leads to carcinoma of the stomach.

Hurst describes the effect of gastritis on the gastric secretion: "The gastric mucous membrane attempts to protect itself against mechanical and chemical irritants by the secretion of

mucus. It is such a weak alkali that its buffer action is hardly appreciable, but it contains sufficient sodium bicarbonate to neutralize some of the gastric juice. At the same time some of the tenacious mucus adheres to the surface of the mucous membrane and blocks the mouths of the secreting tubules, thus reducing the quantity of gastric juice which can gain access to the lumen of the stomach. The inflammation of the gastric mucous membrane depresses the functional activity of its glands. The parietal cells are most delicate so that the hydrochloric acid is the first constituent to be seriously affected. If the healthy stomach produces gastric juice of average or more than average acidity, the reduction of acidity brought about in these three ways is of no importance. If, however, the healthy stomach secretes a gastric juice of less than average acidity, as occurs in individuals with the hyposthenic gastric constitution, achlorhydria results."

Hurst explains a permanent achlorhydria on the basis of an initial inflammation which is so intense that the parietal cells are at once destroyed, or a severe chronic gastritis which permits bacterial invasion resulting in a progressive atrophy of the glands. With the extension of gastritis, he says we get destruction of the hemopoietic and neuromyoietic elements with the resulting pernicious anemia and combined degeneration of the spinal cord.

Once the condition of achlorhydria develops other serious conditions are prone to follow. We have already pointed out

that achlorhydria has been shown in many cases to precede such conditions as pernicious anemia, combined sclerosis of the cord, hypochromic anemia and carcinoma of the stomach. This is pointed out by Hartfall (46) in his discussion of achlorhydria. He goes on to say, however, that the suggestion is not made that mere lack of hydrochloric acid in the stomach is directly responsible for every symptom associated with this disorder; sometimes that may be the case, but more often achlorhydria is simply an indication that something is wrong with the secreting apparatus and combined with this defect in acid secretion are other defects which are more directly concerned with the particular pattern of ill health which may be present.

Miller (80) divides achlorhydria into two groups, congenital and acquired. Both types according to him predispose to gastritis, pernicious anemia, hypochromic anemia, pellegra, arthritis and certain gall-bladder infections. He gives three cases in which the sequence of events was first achlorhydria, then pernicious anemia (the anemia of which was corrected by liver therapy) and later the development of carcinoma of the stomach.

CONCLUSIONS

Changes in the acidity of the gastric secretion indicate a functional or organic disturbance and the proper interpretation of these changes has considerable diagnostic and prognostic significance,

As a diagnostic procedure, the determination of the acidity

curve alone is practically valueless, but if taken in consideration with the entire clinical picture it may prove invaluable. In the interpretation of the acidity values, we must consider not only the pathological conditions which produce typical curves, but also such physiological factors as the automatic regulation of acidity, the psychic state of the patient, the normal variations between individuals, reflex conditions, intoxications and focal infections.

Many systemic infections and toxemias tend to depress the acid secretion of the stomach. Gastritis, therefore, should be considered as a parenchymatous condition analagous with nephritis and hepatitis. Gastric analysis, then, is to be regarded as a functional test of the stomach just as the phenosulphonphthalein excretion and the van den Bergh reactions test the function of the kidney and liver.

Given an inherited constitutional tendency to high or low acidity, gastritis may be a precursor of other diseases. Thus, an insignificant gastritis may lead to peptic ulcer in an individual with hyperacid tendencies. In an individual with low acidity, gastritis may further depress the acid secretion and lead eventually to complete achylia. With achylia this process may destroy the hemopoietic and neuropaetic substances in the stomach, resulting in pernicious anemia, combined sclerosis or hypochromic anemia. If there is also an inherited tendency to malignant change, carcinoma of the stomach may develop.

The acidity of the stomach secretion may be regarded as one of the defense mechanisms of the small intestine. With the breakdown of this mechanism by the process described above, we may find infections of the gall-bladder and liver and even the colon may be affected.

The acid of the gastric juice has a very important function in the body, other than the part it plays in gastric digestion, and disturbances of acidity are potentially dangerous, especially in the event of a superimposed gastritis.

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